Use of dopamine receptor agonists for the treatment of cutaneous tumours, warts and scars

The present invention relates to the use of dopamine receptor agonists, in particular dopamine D_2 receptor agonists, for the local treatment of cutaneous tumours, warts and scars, particularly in combination with dimethyl sulfoxide.

Dopamine receptor agonists, in particular dopamine D_2 receptor agonists, exhibit a dopaminergic action and are mainly employed for the treatment of Parkinson's disease. Some of the dopamine D_2 receptor agonists, such as bromocriptine, for example, are also employed for the treatment of other diseases, such as hyperprolactinaemia, acromegaly or hypophyseal tumours.

Administration of the active substances as antiparkinsonian agents is usually undertaken orally, in the form of tablets. In GB 2 273 873 a topical pharmaceutical preparation that contains bromocriptine as active substance is described for use for the treatment of psoriasis.

Surprisingly it has now been found that topical pharmaceutical preparations of dopamine receptor agonists are suitable for the local treatment of cutaneous tumours, warts and scars.

The invention therefore relates to the use of a dopamine receptor agonist or a pharmaceutically acceptable salt thereof for producing a pharmaceutical preparation for the treatment of cutaneous tumours, warts and scars. The local application, according to the invention, of dopamine

receptor agonists may additionally be assisted by oral administration of dopamine receptor agonists.

Within the scope of this invention, both cutaneous tumours of the preliminary stage of cancer and non-metastasising carcinomas of the skin are covered by the term 'cutaneous tumours'. In particular, it may be a question of actinic keratoses, basaliomas or bowenoids.

The warts that can be treated within the scope of the present invention include, for example, interdigital warts, plane warts, plantar warts, vulgar warts or condyloma.

The scars that are treatable in accordance with the invention include, in particular, swelling-like scars, so-called keloids, such as may arise in cases of skin grafting, for example. Other diseases associated with scarring, such as acne conglobata, scleroderma and xeroderma pigmentosum, for example, may also be treated within the scope of the present invention.

In principle, the use according to the invention encompasses all the dopamine receptor agonists, preferably the dopamine D_2 receptor agonists. These include, in particular, bromocriptine (2-bromo-α-ergocriptine), pergolide (D-6-n-propyl-8β-methylmercaptomethylergolin, selegiline, ropirinole (4-[2-)dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one), pramipexole ((S)-4,5,6,7-tetrahydro-N^6-propyl-2,6-benzothiazolediamine) or cabergolide (6-allyl-N-[3-(dimethylamino)propyl]-N-(ethylcarbamoyl)ergolin-8β-carboxamide). The use of bromocriptine is particularly preferred. Pharmaceutical preparations of these active substances are commercially available in tablet form.

According to a preferred embodiment, the pharmaceutical preparation contains dimethyl sulfoxide (DMSO). The combination of DMSO and a dopamine receptor agonist leads to unexpected synergistic effects in the treatment of cutaneous tumours and warts. Dimethyl sulfoxide is commercially available in extremely pure form (p.a. grade).

Both water-soluble and sparingly water-soluble salts that are generally known to a person skilled in the art enter into consideration by way of pharmaceutically acceptable salts. The topical preparations according to the invention, which contain one or more dopamine receptor agonists as active substance and which are suitable for application on the skin, include ointments, pastes, lotions, cremes, gels or even tinctures.

Production of the preparations is undertaken in known manner, use being made of the known and conventional pharmaceutical adjuvants as well as other conventional excipients and diluents (List et al, *Arzneiformenlehre* Wiss. Verlagsges., Stuttgart, 1985; Sucka et al., *Pharmazeutische Technologie*, Thieme Verlag, Stuttgart 1978).

For example, in the production of an ointment use may be made of organogels (e.g. Vaseline, Plastibase), lipogels (e.g. beeswax), hydrogels (e.g. Aerosil®, bentonites, starch derivatives, polyacrylic acid, polyethylene glycols) or silicone gels by way of ointment base. Vaseline preferably serves as ointment base, in which case the ointment may contain yet other materials, such as fatty alcohols, glyceryl monostearates, triglycerides, alkylene glycols, dimethyl sulfoxide and water. In quite

particularly preferred manner the DAC base creme (Cremor basalis, Deutscher Arzneimittel-Codex), which contains white Vaseline, glycerol monostearate 60, cetyl alcohol, medium-chain triglycerides, macrogol 1000 glycerol monostearate, propylene glycol and water, is used by way of ointment base.

In the production of cremes the ointment bases stated above in combination with relatively large quantities of water may be used, in particular also fats and oils, waxes, fatty acids and esters of fatty acids, long-chain alcohols and emulsifying substances.

The preparations in gel-form include organogels (i.e. hydrocarbon gels, e.g. Vaseline, Plastibase), lipogels (e.g. natural fats, beeswax), hydrogels (e.g. hydroxypropyl cellulose, hydroxypropyl methyl cellulose, Aerosil®, bentonites, starch derivatives, polyacrylic acid, polyethylene glycols), silicone gels or emulsion gels that contain conventional emulsifiers, as well as oleogels that are substantially composed of liquid paraffin with polyethylene or oils and thickeners.

Furthermore, the addition of preservatives, stabilisers, buffering substances, dyestuffs, anti-oxidants etc is possible.

For the production of tinctures for topical application, water or physiologically compatible solvents such as, for example, alcohols (ethanol, propylene glycol or polyglycols), oils or paraffins enter into consideration, for example.

The pharmaceutical topical preparations according to the invention contain the dopamine receptor agonist or a pharmaceutically acceptable salt thereof in a quantity from 0.1 wt.% to 10 wt.%, relative to the pharmaceutical preparation. The content of active substance preferably lies within the range from 0.25 wt.% to 0.5 wt.%.

According to a preferred embodiment, the pharmaceutical preparation contains DMSO in addition to the dopamine receptor agonist. The DMSO may be contained in the pharmaceutical preparation in a quantity amounting to 5-20 wt.%, preferably 10-15 wt.%, relative to the pharmaceutical preparation.

For the purpose of introducing the dopamine receptor agonists into the topical preparations according to the invention, use may be made of commercial active-substance preparations. In this case the tablets may be dissolved in suitable solvents such as ethanol, for example. Bromocriptine tablets or capsules are obtainable, for example, from Novartis Pharma (Pravidel®), Ratiopharm (Bromocriptin-Ratiopharm®) and Hexal/Neurohexal (Bromocrel®).

According to a preferred embodiment, the pharmaceutical preparation for the use according to the invention is present in the form of an ointment that contains bromocriptine or a pharmaceutically acceptable salt thereof in a quantity from 0.25 wt.% to 0.5 wt.%, relative to the pharmaceutical preparation.

Without intending to be tied to a particular theory for explaining the ascertainable effect of dopamine receptor

agonists, particularly in combination with DMSO, the modes of action elucidated in the following will be considered.

The inhibition of fibroblast growth by the dopamine D_2 receptor agonist bromocriptine is known from *in vitro* experiments (Pawlikowski M., Stepien H., Cell Tissues Res 1979l 202(1):165-169; Pawlikowski M. et al., J Neural Transm 1983; 56(1):91-95). The cutaneous tumours listed above have the common factor that they are rich in fibroblasts and that induction by human papilloma viruses is being discussed. More recent investigations have shown that human papilloma viruses primarily induce benign tumours of the skin and mucous membranes, such as warts and condyloma (Bojanovsky A., "*Erreger bedingter Krankheiten*", edited by Jung E.G., *Dermatologie*, Hippocrates Verlag Stuttgart, 1998, pp 136-139). These include plane warts, vulgar warts, plantar warts, fig warts (condyloma). The bowenoid or verrucosis generalisata may develop from the plane warts, with a potential for malignant transformation in the form of prickle-cell carcinoma. It appears that the dopamine receptor agonists, such as bromocriptine for example, may have a dual effect, namely as inhibitors of fibroblast growth and as inhibitors of keratinocyte growth. From a further study it has emerged that bromocriptine may also result in a modulation of the P-glycoprotein which is associated with MDR (multi-drug resistance) (Orlowski et al., Biochem Biophys Res Commun 1998; 244:481-488).

The thesis that bromocriptine presumably has an apoptotic effect on fibroblasts has also been supported by the observation of a female patient who applied the bromocriptine creme onto a swelling-like scar (keloid). The cicatricial keloid, measuring 4 cm, arose after autologous skin grafting. Scars no longer grow and consist

principally of collagen fibres and their producers, the fibroblasts. After four weeks of bromocriptine treatment the scar was barely visible any longer. In this case it may not be a question of an effect on keratinocytes. What is uncertain is whether, in addition to the effect on the fibroblasts, a direct effect on the collagen fibres themselves is also achieved.

Dimethyl sulfoxide (DMSO) is a resorption accelerator and anti-inflammatory, and also exhibits low-grade anaesthetic properties. But, in particular, DMSO also appears to act as an inhibitor of keratinocyte growth. This could represent an explanation of the synergistic effect in the case of the use of DMSO in combination with a dopamine receptor agonist, particularly with respect to the inhibition of keratinocyte growth. It would also be possible that DMSO, which is employed above all for the purpose of improving penetration, develops, by virtue of bromocriptine, an autonomous effect in respect of the epithelial cells of the tumour via the P-glycoprotein membrane transporter.

The pharmaceutical preparation in topical form is applied several times a day, as a rule two to four times a day, onto the affected cutaneous areas. The frequency of application may be adapted as required. The local treatment of cutaneous tumours and warts with the preparation according to the invention may be undertaken together with a medicinal treatment that is matched to the disease. These include, in particular, therapies with activated immune cells, such as have been described in WO 99/50393. According to a preferred embodiment, the topical preparation is assisted by an adjuvant therapy with oral preparations of dopamine receptor agonists.

The invention will be elucidated in more detail in the following on the basis of examples.

Production of a bromocriptine ointment

By way of ointment base the DAC base creme (Cremor basalis, Deutscher Arzneimittel-Codex) was employed, having the following composition:

making up 100 g of preparation:

glycerol monostearate 60	4.0 g
cetyl alcohol	6.0 g
medium-chain triglycerides	7.5 g
white Vaseline	25.5 g
macrogol 1000 glycerol monostearate	7.0 g
propylene glycol	10.0 g
water	40 g

For the production of the ointment, 77 g DAC base creme, 12 g dimethyl sulfoxide and 250 g bromocriptine, dissolved in 11 g ethanol, were employed.

Patient studies

In a 28-year-old female patient with a bowenoid in the genital region, who unfortunately had migraine attacks in the course of the application of activated immune cells, activated immune cells were used in a low dosage together with locally applied bromocriptine ointment. The cellular therapy, which had already been carried out for six months previously and which prevented tumour growth but did not

result in the elimination of the tumour, was able to be brought to an end after two weeks of additional bromocriptine-ointment therapy (ointment from the above example) after disappearance of the tumour. No relapse occurred, even after an observation period of three years.

A 60-year-old male patient with a parvicellular bronchial carcinoma which had been treated for five years with activated immune cells had, in addition, actinic keratoses (a preliminary stage of cancer) and multiple basalioma (a skin cancer which very seldom metastasises) on the trunk and on the face, which were surgically removed at least twice a year. The cellular therapy had clearly reduced the growth of the basalioma; most of them disappeared, some remained in a kind of resting state; likewise the actinic keratoses. After about six months of additional bromocriptine-ointment therapy (ointment from the above example) about half of the cutaneous tumours had disappeared, in part also the actinic keratoses, which evidently necrose more slowly than the basalioma. The cicatricial areas after basalioma excision, which were formerly the site of repeated resection, are inspected by the surgeon every six months. No further surgical interventions on the skin have been carried out for two years.

An 85-year-old male patient who came once a month for the treatment of recurrent infections complained about warts between his toes. They were, inter alia, removed surgically, but they recurred again and again and were very painful. The problems of the unsuccessful treatment or its temporally limited effect and its painfulness are known. After bromocriptine-ointment therapy (ointment from the above example) the warts disappeared after 72 hours. To be

on the safe side, the therapy was carried out for one week; the patient has remained free from recurrence for one year.

A 72-year-old female patient had already had surgery several times every year in the facial region, above all on the bridge/side of the nose. After four weeks of bromocriptine-ointment therapy (ointment from the above example) the operation that was already planned was able to be cancelled on account of the distinct recession of the tumour. After about eight months the formerly distinct swelling and reddening of the bowenoid was only minimally present; bowenoids arising anew in other places also respond to the creme. Although the bowenoid has not yet been eliminated, the result is very satisfactory, since no surgical intervention is required, and the cosmetic result also clearly surpasses that of surgery. An additional therapy with activated immune cells, or additionally oral bromocriptine, would possibly be successful more quickly, but the local high concentration of bromocriptine is definitely an essential factor in the treatment. Oral bromocriptine has a number of side-effects (extending as far as cerebral haemorrhages), which can be avoided by local therapy. It should be mentioned that in the case of prolactin-forming hypophyseal tumours the oral bromocriptine therapy should not be discontinued, since otherwise the genesis of a relapse may occur.

In the case of a 55-year-old female patient with warts between the feet [*sic*] the warts disappeared after about two weeks of application of bromocriptine ointment (from the above example). A relapse occurred after about one year, which was probably a consequence of an error in the scheme of treatment. Following a correct scheme of treatment (mornings and evenings; in the individual case a

rarer or more frequent application may be appropriate) no further relapse has occurred (for over two years).

A 32-year-old female patient with a vulgar wart was able to be treated successfully by application of the bromocriptine-ointment therapy (ointment from the above example) over a period of one week. The patient has had no recurrence for one year.

In the case of a 61-year-old male patient with a plane wart in the temporal region the wart disappeared after bromocriptine-ointment therapy (ointment from the above example) after a few weeks. In this patient, firstly a successful treatment was evident after three weeks, though after two months a relapse occurred with additional adjacent "daughter warts". The latter disappeared within five days as a result of bromocriptine-ointment therapy; the original wart in the temporal region has almost disappeared; the patient has been free from recurrence for four months.

The bromocriptine-containing ointment according to the invention has resulted in a clear recession of cutaneous tumours, warts and scars within a short time, and consequently opens up new and efficient approaches in the treatment of such diseases and related diseases.